REMARKS

Claims 1-3, 5,7-10, 14-15, 17-18, 23-35 and 39-45 were pending after Applicants' earlier response to a Restriction/Election Requirement and further Preliminary Amendment.

In the pending Action, the Office determined that certain claims should be considered withdrawn, and examined only Claims 1, 15, 17, 18, 23-24 and 33-34 on the merits in this office action. Applicants' further comments regarding these withdrawals and an apparent misunderstanding of applicants' intention with respect to the embodiments to be examined are discussed in Section II., below. Specifically, Applicants request reconsideration of the withdrawal of claim 35 (which should remain active and is designated herein as "previously presented").

I. General Comments on Amendments to Claims[1]

A. Introduction of specific substituted benzoyl groups

The following claims/ sections have been amended to recite specific substituted benzoyl groups that substitute the N-terminal residue (vs. the original claim language that referred only to "substituted benzoyl groups":

Claim 1 and Claim 2

description of A1: "…derivatized at the N-terminus with a substituted benzoyl group selected from the group consisting of 2-fluorobenzoyl, 3-fluorobenzoyl, 4-fluorobenzoyl, 2-bromobenzoyl, 3-bromobenzoyl, 4-bromobenzoyl, 2-nitrobenzoyl, 3-nitrobenzoyl, and 4-nitrobenzoyl…"

description of A2: "…derivatized at the N-terminus with a substituted benzoyl group selected from the group consisting of 2-fluorobenzoyl, 3-fluorobenzoyl, 4-fluorobenzoyl, 2-bromobenzoyl, 3-bromobenzoyl, 4-bromobenzoyl, 2-nitrobenzoyl, 3-nitrobenzoyl, and 4-nitrobenzoyl…"

Claim 34

"… wherein the N-terminal amino acid is derivatized by a substituted benzoyl group selected from the group consisting of 2-fluorobenzoyl, 3-fluorobenzoyl, 4-fluorobenzoyl, 2-bromobenzoyl, 3-bromobenzoyl, 4-bromobenzoyl, 2-nitrobenzoyl, 3-nitrobenzoyl, and 4-nitrobenzoyl."

B. Removal of "α-amino nitrogen" language (allegedly new matter)

All claims which had earlier been amended to recite "derivatized at the α-amino nitrogen" have now been amended to recited "derivatized at the N-terminus."

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[1] In their identification of support in the Specification, applicants rely at times on paragraph numbers that were added to the published U.S. application. Applicants believe the Examiner has this document in the PTO file since reference is made in the Office Action to paragraphs numbered in the publication. The publication can be obtained at he USPTO website, at the URL http://appft1.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PG01&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.html&r=1&f=G&l=50&s1=%22200602643 78%22.PGNR.&OS=DN/20060264378&RS=DN/20060264378

C. Language directed to "preventing" diseases

In claim 17, the language "preventing" as applied to cancers or chronic rheumatoid arthritis has been removed, so that the claims are now directed to "a method for "treating or ameliorating cancers or chronic rheumatoid arthritis". Support can be found, for example at paragraph [0276] of the application (see US published application for paragraph numbering).

D. New Claims

New claims 46, 48, and 50 limit claims 1, 15 and 17, respectively to two substituted benzoyl groups.

New claims 47, 49 and 51 further limit claims 46, 48 and 50, respectively to the elected species (SEQ ID NO:64) which has one of the two types of substituted benzoyl groups specified in these parent claims. The claim language corresponds to the earlier claims as follows:

New claim	Corresponding compound of Withdrawn Claim
Claim 47	Claim 14, compound #54
Claim 49	Claim 31, compound #54
Claim 51	Claim 39, compound #54

New claim 52 is directed to a single embodiment of method claim 17, that of inhibiting a manifestation of cancer - - cancer metastasis. Support for this language can be found, for example, at paragraph [0276] (as numbered in the published U.S. application).

No new matter is being added with these amendments. Again, the examples (*e.g.* Experimental Examples 1 and 5-10) describe the efficacy of peptides with substituting benzoyl-groups at their N-terminal amino acid; the original claims further support such language.

Applicants reiterate that they have now further limited claim 1 (as well as claims 2 and 34~~)~~) to those peptides of formula (I) that are derivatized at their N-terminus by a limited group of substituted benzoyl groups: 2-fluorobenzoyl, 3-fluorobenzoyl, 4-fluorobenzoyl, 2-bromobenzoyl, 3-bromobenzoyl, 4-bromobenzoyl, 2-nitrobenzoyl, 3-nitrobenzoyl and 4-nitrobenzoyl.

II. DISCUSSION OF THE RESTRICTION/ELECTION REQUIREMENT

First Applicants, acknowledge the Office's admission that two of the species elections were made in error and are being withdrawn, namely, the requirement to elect from among of different diseases and from among CXCR4 antagonists. However, the Office maintained the

requirement for an election of a species from among peptides with the sequences SEQ ID NO's: 11-68.

The Office has acknowledged Applicants election (with traverse) of Group I (claims 14, 31-32 and 18 and 39) defined in the restriction requirement as being drawn to a pharmaceutical composition comprising, a peptide with the formula X-DLys-Pro-Tyr-Arg-Cit-Cys-Arg, and a method for preventing or treating chronic rheumatoid arthritis ("RA") in subjects by administering to the subject a pharmaceutical composition comprising as an active ingredient a therapeutically effective amount of a peptide. The Office further acknowledged the election of the species of peptide characterized by the sequence SEQ 10 NO: 64.

Applicants do not understand why claim 35 was considered to be withdrawn by the Office as it depends from active claim 34 (which is currently being amended). Claim 35 is directed to two of the derivatizing benzoyl groups recited in claim 34 which have been searched and found to be free of the prior art. Claim 35 is therefore presented herein as an active claim, and the Examiner is requested to consider it.

Applicants believe that despite the language in the Office Action characterizing the elected invention (noted above), and in view of the withdrawal of two of the species election requirements, the elected invention includes method claims to the treatment of cancers and chronic rheumatoid arthritis.

III. REJECTION UNDER 35 U.S.C. § 112, 1ST PARAGRAPH -- LACK OF ENABLEMENT

Claims 17-18 and 33-34 were rejected as failing to comply with the enablement requirement.

Office's Analysis Under *In Re Wands* and Applicants' Response

The Office Action set forth a *Wands* analysis parts of which are restated in varying detail below.

(1) The nature of the invention:

The Action focused in this part of the analysis on the lack of enablement primarily of **prevention** (and/or therapy) of cancers and rheumatoid arthritis using the recited peptides and pharmaceutical compositions.

(2) The state of the prior art:

(a) Preventing vs. Treating Diseases

The Action focused here on the lack of enablement for **preventing** cancers and cited a number of supporting references for its position. The Action spent some time on a number of issues which Applicants believe are not germane to this analysis (*e.g.*, discussion of palliative care to improve quality of life for late stage cancer patients with advanced disease, or a discussion of pain, wasting, nausea and other health problems that result from cancer's progression.).

As for chronic rheumatoid arthritis (RA), the Action discussed the pathophysiology of this condition, the nature of diagnostic tests used for it, and the fact that, in some cases, the precise cause is unknown but rather has a multifactorial nature, the classes of drugs used to treat various symptoms, *etc.* Again, a much of this does not appear directly related to the claim language. The Office's stated position is that "drugs that appear to slow the progression of RA are available" (citing to several sections from the *Merck Manual*).

The Action concluded that

> The art provide guidance as to how to treat cancers and reduce the progression of RA, but do not provide guidance as how to how to determine individuals who are susceptible to cancers and RA.

Applicants Response

Without agreeing with most of the Office's position discussed above, Applicants have amended the claim language to delete any reference to "preventing cancers" or "preventing RA" (see amended claim 17) which results in a change in scope of all the rejected claims so that they do not run afoul of the enablement requirement as far as the *Wands* factors discussed herein are concerned.

(b) Concerns about *In Vitro* and *In Vivo* Studies in Cancer Drug Development

The Office Action goes on to say that "arts indicate the difficulties in going from *in vitro* to *in vivo* for drug development for treatment of cancers." The Action cites Auerbach *et al.* (*Canc. Metastas Rev*, 2000, *19*:167-72, for the proposition that "a major problem in angiogenesis research has been the difficulty of finding suitable methods for assessing the angiogenic response" and goes on to describe in greater detail *in vitro* assays for screening cytokines and some of their limitations as well as certain "difficulties" in quantitating *in vivo* assays. The Office cites Gura T (*Science*, 1997, *278:*1041-42) which is not a peer-reviewed scientific paper by a practicing scientist but rather a piece of reportage by a "writer" whose credentials and

affiliation are not identified, and were presumably not subject to any kind of review for scientific accuracy. Various quotes are selected from Gura such as "the fundamental problem in drug discovery for cancer is that the model systems are not predictive at all" or that

> the results of xenograft screening turned out to be not much better than those obtained with the original models , mainly because the xenograft tumors don't behave like naturally occurring tumors in humans--they don't spread to other tissues, for example.

Further, according to the Office

> ...when patient's tumor cells in Petri dishes or culture flasks and monitor the cells' responses to various anticancer treatments, they don't work because the cells simply fail to divide in culture, and the results cannot tell a researcher how anticancer drugs will act in the body

The Action further cites Jain RK (*Sci Amer*, July 1994, pp58- 65) for the statement that

> the existing pharmacopoeia has not markedly reduced the number of deaths caused by the most common solid tumors in adults, among them cancers of the lung, breast, colon, rectum, prostate and brain

and further discusses difficulties resulting from with the need for therapeutics to disperse throughout the growths in concentrations high enough to eliminate every deadly cell.

The Office concluded that the "art recognizes that going from *in vitro* studies to *in vivo* studies for cancer drug developments are difficult to achieve."

Applicants' Response

Applicants respectfully submit that despite various statements that can be found regarding the complexities of cancer drug development, the fact is that all anti-cancer drug therapies, as well as therapies for RA have always been and continue to be developed using both *in vitro* systems and *in vivo* subhuman animal models. One cannot begin human clinical trials in humans without demonstrating efficacy (in addition to safety, of course) first *in vitro* and then in animal models. Applicants cannot dispute that, from time to time, disappointing results are obtained using some animal models. The Auerbach reference (*supra*) may be considered limited to the angiogenesis setting, as that is Dr. Auerbach's area of expertise. The Examiner certainly should appreciate that individuals publish scientific or lay articles cautioning against over-interpreting results obtained in culture or in animal models. However, such articles only emphasize that, indeed, the state of the art (at the time the present invention) which the Office admits **"provides guidance as to how to treat cancers and reduce the progression of RA,"** was attained by the use of *in vitro* and animal models. For this reason, it would be proper to remove this basis for a conclusion of lack of enablement of the present claims.

(3) The relative skill of *those in the art:*

Applicants have no argument with the Office's conclusion that the relative skill of those in the art of this invention is high.

(4) The predictability or unpredictability of *the art:*

The Office Action again emphasizes here Applicants' use of the term "preventing" in claim 15, wherein there would be a need to determine or predict which subjects are susceptible to cancers and rheumatoid arthritis. The predictability of such determinations in the art are allegedly low.

Applicants' Response

As above, Applicants deletion of the terms "preventing cancers" or "preventing RA" renders moot this aspect of the Office's *Wands* analysis.

(5) The breadth of the claims:

The Action notes that the claims are drawn to a method for preventing or treating cancers or chronic RA, but do not identify a patient population, so they imply that "everyone can be prevented from cancers and chronic rheumatoid arthritis."

Applicants' Response

Again, applicants' amendment of claim 15 to remove "preventing" language renders moot this aspect of the Office's analysis.

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples:

The Action notes that the specification provides no guidance as when to administer the peptide composition in order to prevent RA. The Action discusses Example 5 which is said to disclose the use of 4F-benzoyl-TN-14003 peptide antagonist against human leukemia cells (SUP-T1). Example 6 is said to disclose the inhibitory activity of 4Fbenzoyl-TN-14003 against breast cancer cell migration. Example 7 is said to discloses the antimetastatic activity of 4F-benzoyl-TN-14003 examining cancerous cells and tissues, performed *in vitro*. Example 9 is said to disclose the effect of 4F-benzoyl-TN-14003 on delayed-type hypersensitivity reactions (cellular immunity) in mice. Example 10 is said to disclose the therapeutic effects of 4F-benzoyl- TN-14003 on collagen-induced arthritis in mice. Example 10 further discloses that this molecule significantly inhibited hindlimb swelling, arthritis score and body weight loss.

Again, the Office's basis for its conclusion for lack of enablement resides in its position that the specification does not disclose *how to prevent cancers and RA* while it does disclose the treatment of already existing cancer (described in the Action as "cancerous cells") and RA.

Applicants' Response

Again, this basis for lack of enablement would no longer apply to amended claim 15 (and the other rejected dependent claims) due to deletion of the "preventing" language.

(8) The quantity of *experimentation necessary*

The Office's position is that due to the uncertainty in predicting the patient population susceptible to cancers and RA, in the absence of an appropriate time frame for prevention, undue experimentation would be required to determine if the claimed peptides would be effective in **preventing** cancers and rheumatoid arthritis. The Action notes further that the term **"prevent"** is an "absolute definition" which it interprets as meaning "to stop from occurring" which allegedly requires a *higher standard* for enablement than that required for "'therapeutic' or 'treat' or 'alleviate'" since cancers and RA are "clearly not recognized in the medical arts as being totally preventable conditions."

Applicants' Response

Again, this basis for lack of enablement would no longer apply to amended claim 15 (and the other rejected dependent claims) due to deletion of the "preventing" language.

Applicants conclude that in view of the amendments and remarks above, the present rejection under §112, first paragraph no longer applies to the present claims and may properly be withdrawn.

IV. REJECTION UNDER § 112, 1ST PARAGRAPH -- INADEQUATE WRITTEN DESCRIPTION

Claims 1-2, 15, 17, 18, 23-24 and 33-34 were rejected as failing to comply with the *written description* requirement. The claims are described as being drawn to "a peptide according to formula (I) or a salt thereof wherein amino acid positions are numbered 1-14... A1 is an Arg, Lys, Orn, Cit, Ala, or Glu which is derivatized at the α-amino nitrogen with a substituted benzoyl group or A1 is absent.

The rejection is directed to the lack of **literal** support or **implicit or inherent** support for the language (a) "A1 is absent" and (b) "alpha-amino nitrogen with a substituted benzoyl group". The Office recognizes, so that Applicants need not argue, that the law does not require *in haec*

verba support. But the Action does note that "newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure" (citing MPEP 2163). Applicants understand this rejection to be a "new matter" rejection.

A. "A1 is absent"

The Action states that, in the context of A1 of formula (I), the word "absent" does not appear anywhere in specification. The word "delete" is present in the specification in relation to A1 (citing to paragraph [0012]). The Office seems to believe that, the word "delete" implies that the residue at A1 is present "originally," and then is deleted with a cleavage reaction. The Office states that this is not "in context of A1 being absent originally." The specification also allegedly lacks any implicit or inherent support for the embodiment wherein "A1 is absent."

Applicants' Response

With respect to the language "A1 is absent", the term "deleted" was replaced by the term "absent" merely for the sake of clarity, to rectify a typographical error apparently introduced during translation from the original Japanese language PCT application. It should be fully evident and obvious that a peptide from which residue A1 has been deleted is a peptide in which "A1 is absent". This language replacement is therefore merely semantic, and was done for the sake of clarity. As such, it does not alter the meaning or scope of claims in which "A1 is absent" appears compared to the language "in which A1 has been deleted". Hence, this basis for rejection should be withdrawn.

B. "Alpha-amino nitrogen

According to the Action, the phrase "alpha-amino nitrogen with a substituted benzoyl group" was not found in the specification. As stated in the Action, the word "nitrogen" was provided at paragraph [0281] in relation to alkylating drug of the specification. The words "benzoyl group" was provided at paragraph [0056] in relation to N-terminal amino acid derivatization or non-derivatization of amino group. The only benzoyl group derivatives provided are fluorobenzoyl groups, 4F-benzoyl and 2F-benzyol (see paragraph [0056]). Throughout the specification, the only benzoyl groups provided are 4F-benzoyl and 2F-benzoyl (citing to paragraph [0074], [0079], [0166] and so on). However, 'this is not in the context of 'alpha-amino nitrogen'".

The specification is also said to lack any implicit or inherent support for this language. According to the Office,

> the phrase "alpha-amino nitrogen with a substituted benzoyl group" can be interpreted as only the alpha-amino nitrogen being substituted with the benzoyl group. A1 can be Arg, Lys , Orn, Cit, Ala or Glu.

The Action notes that Lys, Arg, Orn and Cit have extra nitrogens in the amino acid that can react with the benzoyl groups. As stated in the Action, "listing just the fluorobenzoyl groups 4F- and 2F-benzoyl does not encompass the vast number of benzoyl group moiety."

Applicants' Response

As regards the phrase "derivatized at the alpha-amino nitrogen", it is respectfully submitted that the amendment to this language was made for the sake of clarity, to rectify a typographical error apparently introduced during translation of the original Japanese PCT application and did not introduce subject matter not present in the original application. The original translation read "derivatized at the N-terminal" rather than "derivatized at the N terminus"). The application is replete with examples of synthesis (Manufacturing Examples 1-58) that all clearly and explicitly demonstrate that the derivatizing group is linked to the alpha-amino nitrogen of the N-terminal amino acid while all other amino groups (noted above by the Examiner) remain blocked. That is why in the prior Preliminary Amendment, the language was amended to read "alpha-amino nitrogen". However, if the Office does not accept the equivalence of that language, and in order to advance prosecution, Applicants have amended claims 1, 2, 17 and 24 to delete the language "derivatized at the α-amino nitrogen" to read "derivatized at the N-terminus".

Finally, Applicants disagree with the Office's position regarding the scope of the substituted benzoyl groups that are disclosed vs. those claimed. The specification does, in fact, recite a list of suitable substituted benzoyls to be used as N-terminal derivatizing groups in the peptides of the invention. Paragraph [0166] recites, with respect to peptides derivatized at the N-terminus,

> ...substituted benzoyl group (*e.g.*,: 2-fluorobenzoyl, 3-fluorobenzoyl group, 4-fluorobenzoyl group, 2-bromobenzoyl group, 3-bromobenzoyl group, 4-bromobenzoyl group, 2-nitrobenzoyl group, 3-nitrobenzoyl group, 4-nitrobenzoyl group).

To advance prosecution, the claims have been limited by amendment to these foregoing substituted benzoyl groups. In addition, new claims 46, 48 and 50 limit the substituted benzoyl groups to 4-fluorobenzoyl or 2-fluorobenzoyl.

In view of the foregoing amendments and remarks, the rejections for lack of adequate written description may properly be withdrawn.

V. REJECTION UNDER 35 U.S.C. § 103(a) - OBVIOUSNESS

Claims 1-2 were rejected under § 103(a) as being obvious over Tamamura *et al.* (*Biochem Biophys Res Commun, 253*:877-82, 1988) (hereinafter "Tamamura") in view of Fujii *et al.* (WO 02/20561 translated as U.S. Patent No. 7,138,488) (hereinafter "Fujii"). The Action went on to restate the language of claim 1 before discussing the references.

A, Tamamura

According to the Office, Tamamura teaches that T140, the sequence of which is

NH_2-R-R-Nal-C-Y-R-K-DK-P-Y-R-Cit-C-R-COOH (see Figure 1),

is a strong anti-HIV peptide which allegedly meets the sequence limitation of claims 1 and 2. The Action notes, however, a difference between the reference and the instant claims: the reference **does not teach** α-amino nitrogen with a substituted benzoyl group.

B. Fujii

According to the Office, Fujii teaches polypeptides A1-R-A2-C-Y-A3-A4-X-A5-A6-Cit-C-A7 or their salts, and further teaches a peptide T140 that has the sequence

H-R-R-Nal-C-Y-R-K-DK-P-Y-R-Cit-C-R-OH (see Table 1).

Fujii is said to teach that

> the protected amino acid to be used for synthesis of the polypeptide means an amino acid whose functional group is protected by a protecting group according to the conventionally known method, and various kinds of protected amino acids are commercially available". Protecting group for an alpha-amino group of an amino acid is Boc, Fmoc, Tos, NO2, Mtr (benzenesulfonyl group), Pmc or Pbf (benzofuran-6-sulfonyl).

Fuji is further is said to teach that the polypeptide specifically binds to CXCR4 ligand.

C. The Rejection

The Office concluded that it would have been obvious to combine the teachings of Tamamura and Fujii to produce a polypeptide having the same (Tamamura) sequence with the N-terminal amino acid **protected** for synthesizing a polypeptide. One of ordinary skill in the art would be motivated to **protect** the N-terminal amino acid when synthesizing a polypeptide, since it is well known in the art that with a free amine, an amino acid may form a peptide bond to the other free amine, for example ε amino group of lysine. Fujii allegedly teaches that a **protected polypeptide** having a desired amino acid sequence can be obtained. The Office concluded too that there was a reasonable expectation of success because

(1) both cited references teach the same amino acid sequence that is utilized for the same purpose (anti HIV-1 peptide) and

(2) a protected polypeptide allows for a synthesis of desired amino acid sequence.

D. Applicants' Response

Applicants respectfully disagree with the foregoing rejection and analysis, particularly as it could be applied to the presently amended claims, for reasons discussed below.

First, Applicants wish to remind the examiner that relevant amendments to claim 1 are as follows:

> ...A1 is an arginine, lysine, ornithine, citrulline, alanine or glutamic acid which -is derivatized at the N-terminus with a substituted benzoyl group selected from the group consisting of 2-fluorobenzoyl, 3-fluorobenzoyl, 4-fluorobenzoyl, 2-bromobenzoyl, 3-bromobenzoyl, 4-bromobenzoyl, 2-nitrobenzoyl, 3-nitrobenzoyl, and 4-nitrobenzoyl,...
>
> ...if A1 is absent, A2 is arginine or glutamic acid derivatized at the N-terminus with a substituted benzoyl group selected from the group consisting of 2-fluorobenzoyl, 3-fluorobenzoyl, 4-fluorobenzoyl, 2-bromobenzoyl, 3-bromobenzoyl, 4-bromobenzoyl, 2-nitrobenzoyl, 3-nitrobenzoyl, and 4-nitrobenzoyl...

Claim 2 is similarly amended with respect to substituted benzoyl groups.

Applicants submit that while particular chemical groups, such as those disclosed in Fujii are well-known as protecting groups for N-terminal amino acids during peptide synthesis, these chemical groups are typically removed by the end of the reaction, as they are not desired in the final synthetic peptide. It is well accepted in the art that these specific chemical groups are chosen for their ease of cleavage during peptide synthesis. Such groups temporarily mask the characteristic chemistry of the protected functional groups, thus preventing undesirable chemical reactions during peptide synthesis (as discussed in the Office Action).

The protecting groups disclosed by Fujii and noted in the Action **do not include the substituted benzoyl groups** that are recited in the present claims and that constitute the desired substituent in the final peptides. The protecting groups listed by the Office (above) and disclosed in Fujii **do not include** the preferred substituted benzoyl groups, including the preferred fluorobenzoyl groups (such as 4F-benzoyl) that are bonded to the N-terminal residue in the peptides of the present claim.

Indeed, there would be **no** motivation for the skilled artisan to synthesize the claimed peptides (defined by Formula I) which are derivatized (in their final form) at their N-terminus by a limited array of substituted benzoyl groups (such as 4F-benzoyl). This lack of motivation stems from the fact that the effect of such substitution on the biological activity of the peptide could not have been predicted from the prior art.

The present inventors made the surprising discovery that derivatizing a T-140 analog peptide at its N-terminus with a substituted benzoyl group (particularly the 4F-benzoyl group), results in peptides which have potent activity and are particularly useful in the treatment or amelioration of cancer or chronic rheumatoid arthritis in a subject, because these peptides have pharmacological profiles that are superior to those of hitherto known peptides.

Thus, there would have been no reason for the skilled artisan to consider making the claimed peptide nor would that person have had any expectation of success in ending up with an improved anti-cancer or anti-RA peptide. Therefore amended claims 1 and 2 cannot properly be considered as obvious over Tamamura when combined with Fujii. It would be proper to withdraw this rejection.

VI. CONCLUSION

Applicants believe they have responded fully to the Office Action. Applicants respectfully request that the amended claims, remarks and requests be entered. Applicants believe the claims are now in condition for allowance, and await such early notification.

Respectfully submitted,

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